| DECLARATION UNDER 37 C.F.R. § 1.132 OF DR. JOSEPH M. PATTI, PH.D. | | |
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| | Application # | 10/056,052 |
| | Confirmation # | 3946 |
| | Filing Date | 28 January 2002 |
| | First Inventor | PATTI |
| | Art Unit | 1648 |
| | Examiner | Lucas, Zachariah |
| | Docket # | P07069US04/BAS |

I, Dr. Joseph Patti, Ph.D., declare and state as follows:

1. I am the first-named inventor of the above-identified patent application, and I am currently the Vice President of Clinical Research for Inhibitex, a company that specializes in products and research regarding extracellular matrix proteins and monoclonal antibodies generated thereto including those embodied in the present invention. In addition to being a co-inventor of numerous US Patents in this general field, including most recently U.S. Pat. No. 6,288,214 for Collagen Binding Protein Compositions and Methods of Use, U.S. Pat. No. 6,680,195, for Extracellular matrix-binding proteins from Staphylococcus aureus, U.S. Pat. No. 6,685,943, Fibronectin binding protein compositions and methods of use, and U.S. Pat. No. 6,692,739, Staphylococcal immunotherapeutics via donor selection and donor stimulation, and I have also authored or co-authored numerous journal articles in this field. I am thus well familiar with the subject matter of the present invention.

2. The present invention was developed in an effort to obtain a monoclonal antibody recognizing the ClfA protein which could also be shown as protective against *S. aureus* infection. As the Examiner recognizes in the outstanding Official Action, despite the long knowledge of the ClfA protein, such as described in U.S. Pat. No. 6,008,341 cited by the Examiner, no one had previously actually produced a monoclonal antibody to the

ClfA protein, much less one with any reasonable expectation of success in providing protection against staphylococcal infection. While the technology for producing monoclonal antibodies has been long established, such as shown in the Kohler et al. 1975 Nature article cited by the Examiner, it has been very hard to predict with any certainty which monoclonal antibodies to which proteins, or fragments or domains, will result in antibodies capable of afforded protection against infection.

3. A perfect example of the uncertainty in this field is shown in the attached Abstract from the article Ichiman et al., Can J Microbiol. 1991 May;37(5):404-7, attached hereto as Exhibit 1. In that article, the authors disclose the fact that passive protective activities of three different classes of monoclonal antibodies in mice against challenge with strain ATCC 31432 (capsular type I) of Staphylococcus epidermidis were examined, and that while the monoclonal IgM antibody did passively protected mice against challenge with the homologous strain, "monoclonal IgG1 and IgG2b antibodies did not." It is thus very uncertain as to which monoclonal antibodies will function at all to provide adequate protection against infection. It is also uncertain with any given region within a target protein which monoclonal antibody against which target region will be successful in protecting against bacterial challenge.

4. Accordingly, before one actually goes forward with attempting to prepare a monoclonal antibody based on any particular surface protein, there are no guarantees that such an antibody can be adequately produced, much less with any certainty that the resulting monoclonal antibody will have success in achieving protection against

infection. It is also uncertain as to which particular epitope of any particular protein will result in a protective monoclonal antibody. It was thus an unexpected result that monoclonal antibodies raised against the ClfA protein by my inventive group provided excellent results in achieving protection well beyond that which would have been expected by one of ordinary skill in the art.

5. The success of our results has been documented in a recent article published in the journal article, Hall et al., Infect Immun. 2003 Dec;71(12):6864-70, entitled "Characterization of a protective monoclonal antibody recognizing Staphylococcus aureus MSCRAMM protein clumping factor A." A copy of this article is included as Exhibit 2, and a summary of the key results from this article is attached hereto as Exhibit 3. In this article, monoclonal antibody 12-9 as described and claimed in the present application was tested for its ability to immunize mice against infection from *Staphylococcus aureus.* As shown in the article, not only was the monoclonal antibody 12-9 able to inhibit fibrinogen binding to ClfA, the anti-ClfA monoclonal antibody of the invention was observed to protect mice against MRSA-induced mortality. As the data showed, mice treated with the anti-ClfA monoclonal antibodies in accordance with the invention, in one experiment, there were significant differences in the relative survival times between the anti-ClfA treatment groups and control groups in that fifty-seven percent of the mice that received mAb 12-9 survived the bacterial challenge to day 15 ($P<0.0001$, Figure 5A), whereas in contrast, only 10% of the mice treated with the control mAb survived the study period.

6. Additional studies as evidenced in Exhibits 2 and 3 also showed similar results. A study designed to assess the biological impact of inhibiting *S. aureus* binding to fibrinogen in a severe in vivo model of *S. aureus* induced mortality once again showed that mAb 12-9 with inhibitory activity provided the best protection (p=0.006) (Figure 5B) of all the antibodies tested. This trend in data was reproducible in at least three different experiments which all showed the overall protective efficacy provided by the mAb 12-9. To our knowledge, the unexpected beneficial results obtained by use of the monoclonal ClfA antibodies of the present application were not only the first report of a successful monoclonal antibody to ClfA, they were the first report of a monoclonal antibody against **any** cell surface protein from *S. aureus* that demonstrated significant in vivo protection.

I hereby state that all statements made herein based on my own personal knowledge are true and correct and that all statements based on my information and belief are true and correct to the best of my knowledge, and further that all of these statements have been made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

2/28/04
Date

Joseph M Patti
Dr. Joseph M. Patti, Ph.D.